Tetracyclines

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. Classical older :tracyclines

Introduced soon after penicillin G and the sulfonamides, the tetracyclines were once widely used, and still are in some countries. Due to the prevalence of tetracycline-resistant organisms and the availability of effective alternative antibiotics, nowadays tetracyclines are the preferred drugs for a relatively small number of diseases.

Numerous older tetracycline compounds with a similar molecular structure (four benzene rings) and about the same spectrum of activity are available

1 ***Chlortetracycline*** the first tetracycline to be discovered, was isolated from *Streptomyces aureofaciens* in 1944 (Duggar *et al.*, 1948). This is no longer available for oral use.

2 ***Oxytetracycline*** derived from *Streptomyces rimosus*, was reported in 1950

3 ***Tetracycline*** first described in 1953, was prepared from chlortetracycline at Lederle laboratories and was also independently derived from oxytetracycline at Pfizer laboratories

4 ***Demethylchlortetracycline or demeclocycline*** was obtained from a mutant of Duggar's original strain of *Streptomyces aureofaciens* and reported in 1957.

5 ***Methacycline (6-methylene-5-hydroxytetracycline)*** was prepared in the Pfizer laboratories.

6 ***Lymecycline (tetracycline-L-methylene-lysine)*** is a compound of tetracycline and an amino acid (Whitby and Black, 1964). It was developed in Italy and is not available in Australia or the USA.

7 ***Doxycycline (alpha-6-deoxytetracycline)*** developed by Pfizer laboratories, is available as both doxycycline monohydrate and doxycycline hyclate Its main advantage is increased oral absorption and a prolonged serum half-life

8 ***Minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline)*** (Redin, 1967).

Tetracycline compounds are mainly marketed for oral administration, but preparations of doxycycline and minocycline for i.v. administration are available.

Two more soluble compounds have been introduced specially for parenteral use

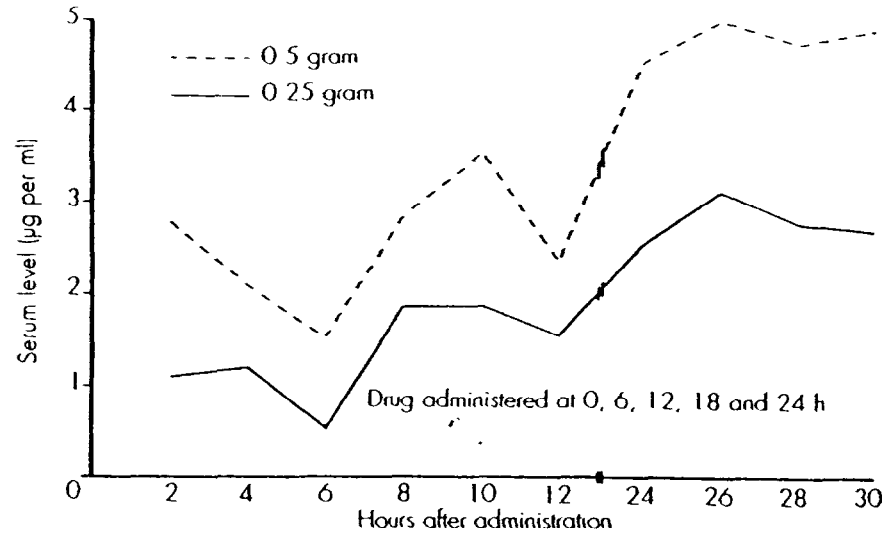

Fig. I.27.
Average serum concentrations following oral administration of 0.25 g and 0.5 g of tetracycline to adults 6-hourly. (Redrawn after Welch, 1954, with permission.)

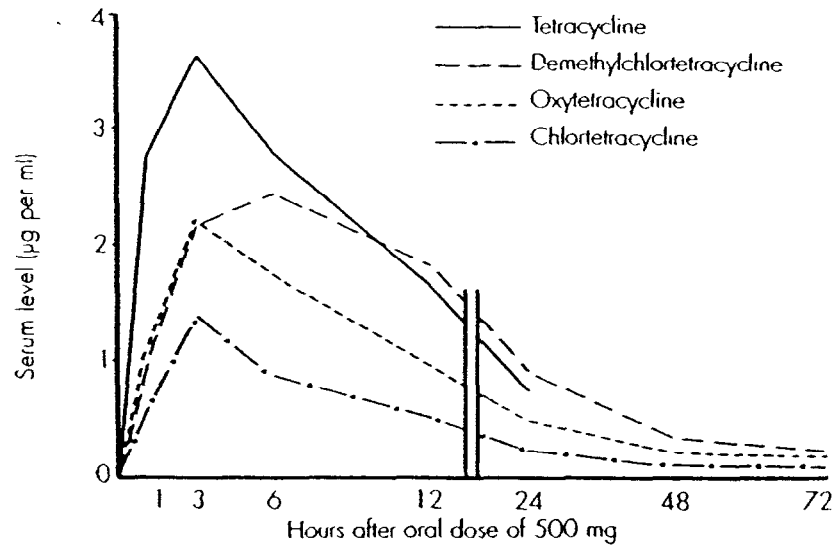

Fig. I.28.
Mean concentrations of four tetracycline antibiotics in serum of normal subjects after single oral doses of 0.5 g equivalents of their hydrochlorides (Redrawn after Finland and Garrod, 1960, with permission from the BMJ Publishing Group.)

cations, such as calcium and aluminum, antacids, milk or milk products in the gastrointestinal tract, also reduces absorption of this drug. In addition, simultaneous administration of ferrous sulfate greatly impairs the absorption of tetracycline from the intestinal tract (Neuvonen *et al.* (1970). There is some evidence that cimetidine may reduce the absorption of tetracycline, possibly because tetracycline requires a low gastric pH for dissolution (Cole *et al.*, 1980; Rogers *et al.*, 1980). The serum half-life of tetracycline after oral administration is abut 7 h (Wood *et al.*, 1975)

2 Doxycycline

Doxycycline is almost completely absorbed in the duodenum after oral administration, and it has a more prolonged serum half-life (18–22 h). After oral administration the peak serum level is usually obtained 2–3 h later. Neuvonen *et al.* (1970) obtained a peak serum level of 3.0 µg per ml after an oral dose of 200 mg doxycycline. After an identical dose, Welling *et al.* (1977) detected peak serum levels of 5.0–5.4 µg per ml at 3–4 h in fasted subjects and these levels fell to 2.9–4.0 and 1.3–2.2 µg per ml after 8 and 24 h, respectively. These authors also noted that serum levels of doxycycline were only reduced by 20% if the dose was given with a meal, whereas serum levels of tetracycline were reduced by about 50%. It was estimated that the mean serum doxycycline level obtained on a regimen of 200 mg daily taken on an empty stomach would be 4.4 µg per ml, and this would only drop to 4.0 µg per ml if the drug was taken with

meals. All tetracyclines form complexes with metal ions in food but doxycycline complexes are unstable in the acid contents of the stomach, so that this drug enters the duodenum in a free state where it is absorbed. However, metal complexes formed in the alkaline contents of the small bowel, into which doxycycline diffuses as part of its mode of excretion (p. 732), are stable and are not absorbed. This explains why simultaneous ingestion of food does not inhibit the absorption of doxycycline from the upper gastrointestinal tract (Whelton *et al.*, 1974).

The absorption of doxycycline is impaired by the presence of ferrous sulfate (Neuvonen *et al.*, 1970) and by subsalicylate bismuth given simultaneously or 2 h before doxycyline (Ericsson *et al.*, 1982). The bioavailability of doxycycline is not reduced by the concomitant administration of ranitidine, but serum levels of doxycycline are lowered if the drug is taken together with aluminum magnesium hydroxide (Deppermann *et al.*, 1989). Aluminum hydroxide taken orally also lowers the serum levels after i.v. doxycycline administration. This interaction may be due in part to an interference of aluminum ions with the enteric reabsorption of doxycycline (Nguyen *et al.*, 1989). If a patient is treated by both doxycycline and rifampicin (p. 693) the serum doxycycline levels may be lower, presumably due to increased hepatic metabolism of the drug (Colmenero *et al.*, 1994).

When a single oral dose of 0.5 g doxycycline was administered after breakfast, a mean peak serum level of 15.29 μg per ml was obtained at 4 h and this fell to levels of 6.60, 3.42, 1.24 and 1.0 μg per ml after 24, 48, 72 and 96 h, respectively (Adadevoh *et al.*, 1976). The fluorometric method used in this study may have resulted in higher serum levels than those obtained by microbiological assay. Nevertheless, Marlin and Cheng (1979) detected a mean peak serum level of 15.41 μg per ml in volunteers given an oral 600-mg dose of doxycycline as estimated by a microbiological method. After a 200-mg i.v. infusion of doxycycline, a peak serum level of 5–10 μg per ml is usually attained (Alestig, 1973), which falls slowly and levels ranging between 1 and 2 μg per ml persist for 24 h (Klastersky *et al.*, 1972). Gnarpe *et al.* (1976) studied serial serum levels after a 200-mg dose given by infusion over 30–45 min; following this infusion mean serum levels of 8.32, 2.98 and 1.32 μg per ml were obtained at 2, 24 and 48 h, respectively.

Minocycline

Similar to doxycycline, minocycline is essentially completely absorbed after oral administration. Its absorption also does not seem to be significantly impaired by administration with food or milk (Smith *et al.*, 1984). After a 150 mg oral dose in adults, an average peak serum level of 2.19 μg per ml is reached in 2 h, which progressively falls to 1.85 μg per ml at 4 h, 1.40 μg per ml at 8 h, and 0.53 μg per ml at 24 h. The drug may be detected in serum for up to 48 h after this single oral dose (Steigbigel *et al.*, 1968a). After an oral loading dose of 200 mg minocycline, peak serum levels occur after 2–4 h and are usually in the range of 2–4 μg per ml (Cartwright *et al.*, 1975; Wood *et al.*, 1975). Following this dose a serum level of about 1 μg per ml is still detectable after 24 h (Cartwright *et al.*, 1975). If after an initial oral dose of 200 mg a dose of 100 mg every 12 h is continued, serum levels are maintained in the range of 2.3–3.5 μg per ml (MacDonald *et al.*, 1973). Very similar results were obtained by Carney *et al.* (1974). When an oral dose of 100 mg minocycline was given twice-daily, peak serum levels were reached after 5 days and these were significantly higher in women (mean 3.4 μg per ml) than in men (mean 2.45 μg per ml) (Fanning *et al.*, 1977). This is probably related to the smaller size of women. A significant inverse correlation has been demonstrated between body surface area and serum concentrations (Bernard *et al.*, 1971; Fanning *et al.*, 1977), but in another study this was not always demonstrable (Gump *et al.*, 1977).

When a 100-mg dose of minocycline dissolved in 200 ml of 5% dextrose in water is infused over 30 min, a mean peak serum level of 8.75 μg per ml is attained immediately after infusion and levels of 3.37, 1.96, 1.32 and 0.81 μg per ml are detected 4, 12, 24 and 36 h later, respectively (Welling *et al.*, 1975). If a dose of 200 mg dissolved in 500 ml is infused daily over a period of 1 h, serum levels of 1–4 μg per ml are maintained (MacDonald *et al.*, 1973). Similar results were obtained when the same dose was infused over 6 h but mean serum level of 6.2 μg per ml was reached immediately on cessation of the infusion (Carney *et al.*, 1974). The serum half-life of minocycline is approximately 13 h (Bernard *et al.*, 1971; Carney *et al.*, 1974, Cartwright *et al.*, 1975).

4 *Rolitetracycline and rolitetracycline nitrate*

After a single i.v. injection of 275 mg of rolitetracycline, the initial serum level was almost ten times higher than the peak level attained after oral administration of 250 mg of tetracycline. This serum level fell rapidly to about 2–4 μg per ml 2 h after injection. However, therapeutically